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【 CASE REPORT 】

Autologous Hematopoietic Recovery after Unrelated Umbilical Cord Blood Transplantation with Myeloablative Conditioning for Acute Myelogenous Leukemia

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Abstract:
Autologous hematopoietic recovery after allogeneic hematopoietic cell transplantation (allo-HCT) is rare in patients who receive myeloablative conditioning (MAC). Autologous hematopoietic recovery suggests graft rejection, leading to concerns about subsequent disease relapse. We herein report a rare case of a patient with acute leukemia who experienced autologous hematopoietic recovery after cord blood transplantation (CBT) with total body irradiation-based MAC. Chromosomal abnormalities were repeatedly detected without any disease relapse for eight months. The accumulation of similar cases is required to accurately assess the incidence and clinical outcomes of autologous hematopoietic recovery after CBT with MAC.

Key words: autologous hematopoietic recovery, myeloablative conditioning

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Introduction

Allogeneic hematopoietic cell transplantation (allo-HCT) is considered to be a curative treatment for hematological diseases and is now indicated for use worldwide (1). However, various adverse events frequently occur following allo-HCT, and the achievement of donor cell engraftment is critically required for a successful allogeneic anti-leukemia/lymphoma effect.

Historically, myeloablative conditioning (MAC) regimens, such as high-dose total-body irradiation (TBI) with cyclophosphamide (CY), have been widely used to achieve the sustained engraftment of donor cells. In general, the risk of graft failure may be increased in allo-HCT from alternative donors or with reduced-intensity conditioning (RIC) regimens (2-6). Thus, TBI-based conditioning is considered to be important for ensuring sufficient immunosuppression to prevent graft failure.

TBI is known to enhance the possibility of neutrophil engraftment in cord blood transplantation (CBT), regardless of the conditioning intensity (7). Therefore, autologous hematopoietic recovery after allo-HCT is extremely rare following allo-HCT with TBI-based MAC due to its strongly immunosuppressive and myeloablative profile, and the development of autologous recovery suggests graft rejection, leading to concerns about subsequent disease relapse (8).

We herein report a rare case of a patient with acute leukemia who experienced autologous hematopoietic recovery after CBT with TBI-based MAC and repeatedly showed different chromosomal abnormalities without any disease relapse for eight months. In addition, we present a literature review regarding autologous hematopoietic recovery after MAC.

Case Report

A 39-year-old man without any remarkable medical his-

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tory was shown to have slight leukopenia and thrombocytopenia at a routine medical check about 3 years before referral to our department. Thereafter, he had been regularly followed-up by a primary care physician. His bicytopenia gradually worsened until blasts appeared in his peripheral blood; at that point, he was referred to our department. The blood test showed severe pancytopenia with a white blood cell (WBC) count of 1.3×10^9/L (blasts 11%, neutrophils 32%), hemoglobin 143 g/L, and platelet count of 0.85×10^9/L. The level of WT1 mRNA was 5.8×10^3 copies/μgRNA in his peripheral blood. His bone marrow (BM) examination demonstrated hyper-cellularity, with 62.6% blasts with tri-lineage dysplasia. The leukemic cells showed CD13+, CD33+, CD34+ and HLA-DR+ with an abnormal karyotype of 46, XY, der(2)t(2;11)(p25;q13) in 3 cells; 46, XY, der(21)t(11;21)(q13;p11.2) in 2 cells; and 46, XY in 15 cells, findings that were compatible with acute myeloid leukemia with myelodysplasia-related changes.

He received induction therapy including 12 mg/m^2/day [intravenously (iv)] of idarubicin hydrochloride (IDR) for 3 days and 100 mg/m^2/day iv of cytarabine (AraC) for 7 days, but the blast cells increased simultaneously with neutrophil recovery. He subsequently underwent salvage therapy including 2000 mg/m^2/day iv of AraC twice daily for 4 days and 7 mg/m^2/day iv of mitoxantrone hydrochloride (MIT) for 2 days. However, the blast cells in his peripheral blood persisted. Next, he was treated with 10 mg/m^2/day [subcutaneously (sc)] of AraC twice daily for 14 days along with 14 mg/m^2/day iv of aclarubicin hydrochloride (ACR) for 4 days, but the blast counts rapidly increased. Finally, he received 3 mg/m^2/day iv of gemtuzumab ozogamicin (GO). However, hematological complete remission could not be achieved. His BM examination showed hypo-cellularity, including 34.4% blast cells with tri-lineage dysplasia. In contrast, chromosomal analyses demonstrated a normal karyotype every examination after the induction therapy.

Therefore, we offered to perform CBT, since he had neither any suitable related donors nor sufficient time to coordinate unrelated volunteer donors. He was treated with TBI at 2 Gy/fraction twice daily from day -2 to 0 and 60 mg/kg/day of CY on days -6 and -5 as myeloablative conditioning and received a 4/6 HLA-matched cord blood unit from a male donor containing 2.6×10^7/kg total nucleated cells and 0.56×10^5/kg CD34+ cells. As prophylaxis for graft-versus-host disease (GVHD), 3 mg/kg/day cyclosporine (CSA) was continuously administered from day -1, with short-term methotrexate (MTX; at 10 mg/m^2/day on day 1 and 7 mg/m^2/day on days 3 and 6).

His absolute neutrophil count (ANC) did not increase during the first four weeks after CBT. On day 28 after CBT, his BM examination showed apparent hypo-cellularity, including 2.6% blast cells and 49.6% macrophages with hemophagocytosis. Furthermore, chromosomal and chimerism analyses revealed that recipient-derived cells accounted for 95.1% of the BM cells, with a complex karyotype of 46, XY, t(5:13)(q11.2:q32), add(6)(q11), add(7)(p11.2), add(20)(q11.2) in 7 cells; 46, XY, ?inv(5)(p15q11.2) in 3 cells; and 46, XY in 2 other cells, suggesting primary rejection of donor cells. Granulocyte-colony stimulating factor was continued at a dose of 250 μg/day until 34 days after CBT, when an ANC of ≥500/μL was achieved.

The recovery of $>0.2\times10^9$/L platelets without any transfusions and ≥10‰ reticulocytes was observed 43 days after CBT. He did not experience any grade of acute GVHD (Figure). BM examinations were performed on days 55, 97, 132, 174 and 223 after CBT, which confirmed his autologous hematopoietic recovery with <5% of donor-derived chimerism. These examinations revealed that his BM showed normal cellularity without any evidence of leukemia relapse but with multi-lineage dysplasia. A different chromosomal abnormality was detected at every BM examination, suggesting that no clonal abnormality had evolved during this period (Table 1). He was carefully observed without any interventions. However, leukemic cells with the same surface markers (CD13+, CD33+, CD34+ and HLA-DR+) appeared and increased on day 258 after CBT (19.6% in BM and 5% in peripheral blood). One of the clones detected on day 223 might have evolved into a leukemic clone, since del(16) was repeatedly detected after the leukemic relapse.

He received remission induction therapy including 100 mg/m^2/day iv of cytarabine for 7 days and 80 mg/m^2/day iv of etoposide for 5 days and 5 mg/m^2/day iv of mitoxantrone hydrochloride for 3 days. from day 272 after CBT. On day 478 after the first round of CBT, he received allo-HCT a second time from a haplo-identical related donor following 30 mg/m^2/day fludarabine phosphate from days -9 to -4, 3.2 mg/kg/day busulfan from days -7 to -4, and 140 mg/m^2/day melphalan on day -2. He achieved hematological complete remission after the second allo-HCT procedure, and thereafter, his chromosomal study revealed a normal karyotype, and the chimerism analysis demonstrated that >99% of his hematopoiesis was derived from the second donor.

Discussion

We encountered a patient with AML who experienced autologous hematopoietic recovery following graft rejection after CBT, associated with various abnormal karyotypes in every BM examination without any clonal evolution for eight months.

Neutrophil engraftment after allo-HCT can be achieved in >90-95% of cases from an unrelated BM donor, but the possibility of engraftment in CBT is known to be lower, and more days are required to achieve neutrophil engraftment than with a related donor (7, 9). The dose of infused cells in a CB unit has been established as a critical factor for the achievement of neutrophil engraftment. In general, CB units with $>2.5\text{-}3\times10^7$ TNC/kg or $>1\times10^5$ CD34+ cells/kg are preferred to avoid the risk of graft failure (10-14). Whether TNC or CD34-positive cells are most important for donor engraftment is debatable, but selecting a unit based on the CD34 cell dose rather than on TNC is considered best if a

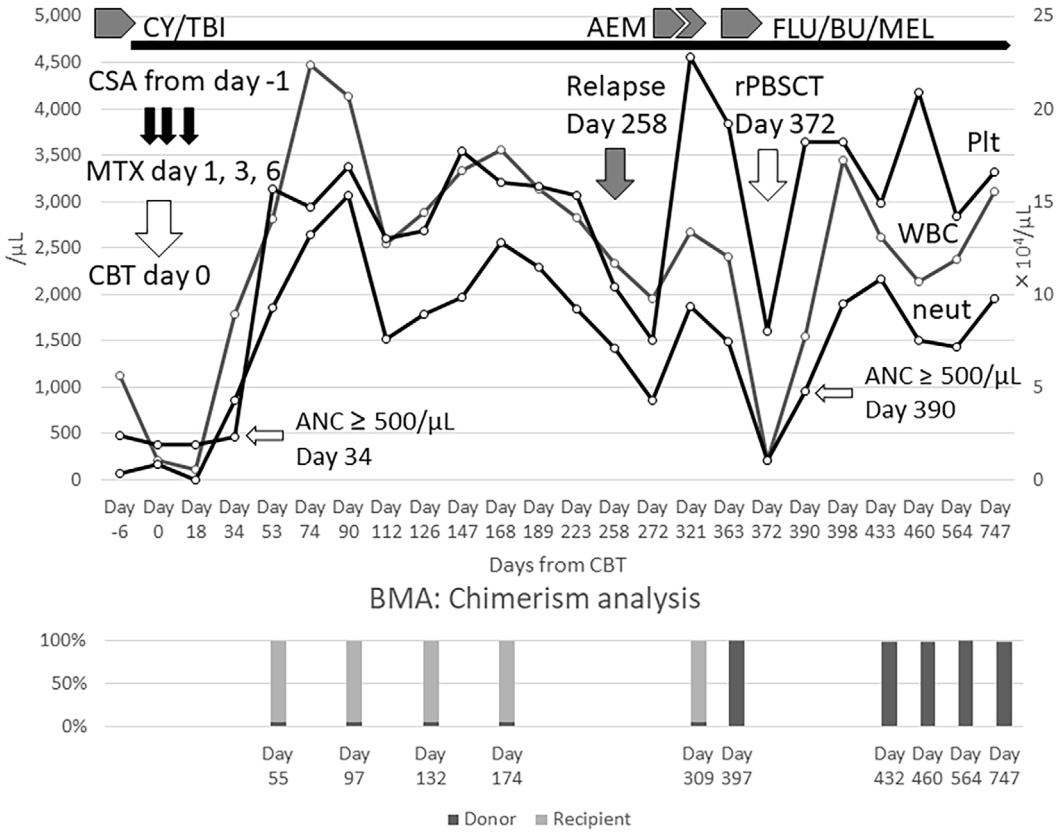

Figure. Clinical course after CBT. The clinical course and results of a chimerism analysis after CBT in this patient. AEM (cytarabine, etoposide, mitoxantrone hydrochloride), ANC: absolute neutrophil count, BMA: bone marrow aspiration, BU: busulfan, CSA: cyclosporine, CBT: cord blood transplantation, CY: cyclophosphamide, FLU: fludarabine phosphate, MEL: melphalan, MTX: methotrexate, Plt: platelet, rPBSCT: peripheral blood stem cell transplantation from related donor, TBI: total body irradiation, WBC: white blood cell, neut: neutrophil

CB unit with an optimal cell dose is not available (15). HLA-disparity between the recipient and CB unit is also reported to be an important influential factor (16), although the impact is controversial. In addition, the selection of a conditioning regimen is also critical for achieving donor engraftment in CBT. TBI is reported to favorably affect neutrophil engraftment, especially in 4/6 or less HLA allele-matched CBT (7). However, a non-TBI regimen with fludarabine, busulfan, and melphalan has also been investigated for its utility in overcoming the reduced possibility of engraftment and a survival in CBT (17). The current patient received a CB unit with a relatively low number of CD34-positive cells, although TBI was given for 4/6 HLA-matched CBT, which might have contributed to his graft rejection.

RIC is less myeloablative than MAC, and autologous hematopoietic recovery might be more frequently observed in transplant patients. For example, recipients with aplastic anemia who experienced autologous hematopoietic recovery after receiving a RIC regimen demonstrated a survival comparable to that in patients who experienced donor engraftment (18). In contrast, MAC is considered to destroy autologous hematopoietic systems. Therefore, graft rejection usually results in persistent severe pancytopenia, leading to unfavorable non-relapse death. To our knowledge, there have been only a few reports (Table 2) of autologous hematopoietic recovery following MAC (19-23). In the 1990s, autologous recovery was often reported in recipients with chronic myeloid leukemia who received BM transplantation. Of them, five cases remained in remission without bcr-abl detection, while the others experienced disease relapse within a few months to years (Table 2). All of the recent cases with autologous hematopoietic recovery, including the current case, received CBT, although this might be due to publication bias. Regardless, through a questionnaire survey, the Japanese Society of Hematopoietic Cell Transplantation (JSHCT) identified 42 recipients who experienced graft rejection and had chromosomal abnormalities among 59,063 allo-HCT recipients between 1974 and 2016. Although the donor source was not reported and the actual incidence was unknown, autologous hematopoietic recovery with chromosomal abnormality was still considered a rare event (24).

The detection of novel chromosomal abnormalities in the present patient raised greater concerns about the development of therapy-related myelodysplastic syndrome (MDS)/leukemia than relapse of the original disease. However, these abnormalities subsequently disappeared, and clonal evolution was not suggested during the clinical course. Since no identical chromosomal abnormalities were found after the first

Table 1. Chromosomal Abnormalities Detected at Each Time Point after Cord Blood Transplantation.

	Karyotype
day 28	46, XY, t(5;13)(q11.2;q32), add(6)(q11), add(7)(p11.2), add(20)(q11.2)[7]/46XY, XY?inv(5)(p15q11.2)[3]/46, XY[2]
day 55	46, Y, t(X;17)(p22.1;q11.2)[1]/46, XY, t(1;8)(q32;q24),del(20)(q1?)[1]/46, XY[6]
day 97	46, XY, t(7;22)(p13;q13)[1]/46, XY, add(12)(p11.2), add(19)(p11), add(21)(p11.2)[1]/46, XY[6]
day 132	46, X, t(Y;1)(q12;p22)[1]/46, XY, t(1;10)(q21;p15), ?t(14;22)(q32;q13), del(20)(ql?)[1]/46, XY[10]
day 174	46, XY, t(1;14)(p11;11.2)[1]/46, XY, t(6;11)(q11;p11.2)[1]/46, XY[3]
day 223	46, XY, t(3;14)(p21;q32), del(9)(p?), del(9)t(9;13)(p24;q12), add(13)(q12), del(16)(q?)[5]/
	46, XY, add(2)(q31), add(4)(q21), add(10)(q22), add(12)(q24.1), add(22)(q11.2)[1]/
	46, XY, add(3)(q21), add(5)(q31), add(7)(p22), -16, add(p11.2), -17, -19, -20, +4mar[1]/46, XY[7]
day 258	46, XY, del(16)(q?)[4]/46, idem, t(3;14)(p21;q32), del(9)(p?), der(9)t(9;13)(p24;q12), add(13)(q12)[5]/
	46, XY, t(1;3)(q21;p25)[1]/46, XY, t(18;20)(p11.2;q11.2), add(21)(p11.2)[1]/46, XY[5]
day 309	46, 46, del(16)(q?)[2]/46, XY, add(2)(q21), add(4)(p11), add(7)(p11.2), add(13)(q12)[1]/
	46, XY, add(7)(q32), add(9)(q12), add(16)(q22), add(21)(q22), add(22)(q11.2)[1]/46, XY[6]
day 357	46, XY, del(16)(q?)[1]/46, XY, ?t(1;13)(q25;q24), add(10)(q22)[1]/
	46, X, -Y, del(2)(q?), -7, -9, add(11)(q13), add(12)(p11.2), -17, -20, +5mar[1]/46, XY[5]

Different complex karyotype every time due to TBI. TBI: total-body irradiation

Table 2. Reports of Autologous Hematopoietic Recovery in MAC Cases since 1998.

Pt	Disease	Donor source	Conditioning	Time to autologous recovery	Outcomes	Ref
1	CML	MUD-BM	TBI-CY	mixed in 6 months, full in 18 months	7 years in remission	19
2	CML	MRD-BM	TBI-CY	mixed in 4 months, full in 20 months	25 months in remission	20
3	CML	MRD-BM	TBI-CY	mixed in 1 month, full in 3 months	relapse in <1 year	21
4	CML	MMUD-BM	TBI-CY	full in 1 month	relapse in 3 years	21
5	CML	MUD-BM	TBI-CY	full in 3 months	relapse in 3 years	21
6	CML	MUD-BM	TBI-CY	mixed in 1 month, full in 2 months	relapse in 6 months	21
7	CML	MMUD-BM	TBI-CY	mixed in 1 month, full in 2 months	relapse in <1 year	21
8	CML	MRD-BM	TBI-CY	full in 3 months	MDS in 1.5 year	21
9	CML	MUD-BM	TBI-CY	75% in 3 months	relapse in <1 year	21
10	CML	MUD-BM	TBI-CY	full in 3 months	relapse in 6 months	21
11	CML	MUD-BM	TBI-CY	mixed in 1 month, full in 3 months	relapse in 2 years	21
12	CML	MUD-BM	TBI-CY	mixed in 1 year	death in 2.5 years	21
13	MPN	MMRD-BM	BU-CY	mixed in 1 month, full in 14 months	5.5 years in remission	22
14	PhALL	CB	TBI-CY	full in 1 month	remission in 5 years	23
15	PhALL	CB	TBI-CY	full in 1 month	relapse in 1 year	23
16	CML-BC	CB	TBI-CY	2 months	Residual disease in 6 months	23
17-58	ALL in 13 AML in 10 CML in 7 Others in 12	Unknown	TBI ≥8 Gy in 30 patients, TBI <8 Gy in 10, no TBI in 2	A median of 2 months to chromosomal abnormality	relapse in 22 patients, 2nd HCT in 4, remission in 15, death in 1	24

MAC: myeloablative conditioning, BC: blastic crisis, Bu: busulfan, CB: cord blood, CML: chronic myeloid leukemia, CY: cyclophosphamide, MDS: myelodysplastic syndrome, MMRD: HLA-mismatched related donor, MMUD: HLA-mismatched unrelated donor, MUD: HLA-matched unrelated donor, MRD: HLA-matched related donor, PhALL: Philadelphia-chromosome positive acute lymphoblastic leukemia, TBI: total body irradiation, HCT: hematopoietic cell transplantation

CBT session, we believe that the patient experienced autologous hematopoietic recovery rather than MDS relapse. However, we were unable to deny the possibility that novel therapy-related chromosomal abnormalities developed seven months after CBT rather than the recurrence of original MDS, based on the chromosome abnormalities.

The repeated detection of chromosomal abnormalities after autologous hematopoietic recovery resembles what oc-

curs after exposure following nuclear accidents (24, 25). A lethally neutron-irradiated nuclear accident victim in Japan received CBT with anti-thymocyte globulin as a conditioning regimen (24). Neutrophil recovery was achieved at 15 days after CBT, but cytogenetic studies revealed mixed chimerism followed by autologous hematopoietic recovery. Repeated chromosomal analyses of the sternal and iliac BM showed that various non-clonal complex abnormalities from 20% to 80% in a single cell (25). In a victim of the 1986 accident at Chernobyl, a very high frequency of translocations was observed over 30 years (26). In a recent report from the JSHCT, TBI was administered to 40 of 42 recipients who experienced autologous recovery with chromosomal abnormalities (24). Of them, 20 experienced disease relapse, but 15 were alive in remission with a 46% 5-year overall survival (24). Thus, the detection of chromosomal abnormalities did not always suggest MDS or leukemic cells, and the findings should be interpreted and followed-up with caution.

In summary, we experienced a rare case of autologous hematopoietic recovery after CBT using MAC that showed non-clonal chromosomal abnormalities. The further accumulation of similar cases is required in order to accurately assess the incidence and clinical outcomes.

The authors state that they have no Conflict of Interest (COI).

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